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Metabolic-inflammatory status as predictor of clinical outcome at 1-year follow-up in patients with first episode psychosis

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Highlights

- In 42 first-episode psychosis patients, C-reactive protein and metabolic variables were combined in 3 metabolic factors.
- Symptoms severity and treatment response were measured at 1-year follow-up.
- Factor 1, accounting for baseline C-reactive protein, BMI and triglycerides, predicted symptoms severity and treatment response at 1-year follow-up.
- The inflammatory-metabolic status at the onset of psychosis may be a predictor of clinical outcome.

Abstract

Background: Metabolic abnormalities and peripheral inflammation have been increasingly reported in patients at the onset of psychosis and associated with important physical health disorders and increased mortality. However, the impact of an abnormal metabolic-inflammatory status on the psychiatric outcome of these patients has not yet been investigated.

Objectives: The aims of this study were 1) to explore whether, in a sample of patients at their first episode of psychosis (FEP), an overall metabolic-inflammatory status may be measured, by

combining metabolic and inflammatory variables in metabolic-inflammatory factors; 2) to explore the association between these factors and clinical outcome at 1-year follow-up (FU), in terms of symptoms severity and treatment response.

Methods: In this longitudinal study we recruited 42 FEP patients and 46 healthy controls (HC) matched with patients for age, gender and ethnicity. At baseline (T1) we measured high sensitivity C-reactive protein (hsCRP) as biomarker of inflammation, and body mass index (BMI), lipid profile and gluco-metabolic parameters (glycated hemoglobin (HbA1c) and fasting glucose) as metabolic variables. A principal component analysis (PCA) was then used to reduce the dimensionality of the dataset accounting for both inflammation and metabolic status. In FEP patients, we assessed symptoms severity at T1 and at 1-year FU (T2) as well as treatment response to antipsychotics at T2.

Results: at T1, FEP showed higher HbA1c (p=0.034), triglycerides (TG) (p=0.045) and BMI (p=0.026) than HC. PCA identified 3 factors: factor 1 accounting for hsCRP, TG and BMI, factor 2 accounting for LDL and cholesterol, and factor 3 accounting for fasting glucose and HbA1c. Factor 1 was associated with T1 negative symptoms severity (p=0.021) and predicted T2 positive (p=0.004) and overall symptoms severity (0.001), as well as general psychopathology (p<0.001) and T2 treatment response (p=0.007).

Conclusion: In this sample of FEP patients, inflammation and metabolism, closely correlated at the onset of psychosis, proved to play a key role as predictors of the clinical course of psychosis when combined in a single factor. These findings offer an important potential target for early screening and interventions.

Keywords: inflammation, metabolism, predictor, first episode psychosis, clinical outcome, BMI.

1. Introduction

Metabolic abnormalities and peripheral inflammation have been increasingly reported in patients with psychosis, often already at illness onset (Hepgul et al., 2012; Pillinger et al., 2017b; Russell et al., 2015). The combination of overweight, dyslipidaemia, hyperglycaemia and peripheral immune activation can lead to severe cardiovascular diseases, like metabolic syndrome, and to increased mortality in patients with psychosis (Leonard et al., 2012; Ringen et al., 2014). However, the consequences of this abnormal metabolic-inflammatory state for the psychiatric/mental health clinical outcome in patients at the onset of psychosis remain undetermined.

Recent evidence from our group has shown that increased baseline peripheral inflammatory markers, such as interleukin (IL)-6, predict poor treatment response at 3-month follow-up in patients with first episode psychosis (FEP) (Mondelli et al., 2015). Similarly, metabolic abnormalities in patients with bipolar disorder have been reported to be associated with worse psychiatric clinical outcome, including higher number of relapses, hospitalizations and more impaired cognitive functioning (Bai et al., 2016; Calkin et al., 2009; Fagiolini et al., 2003). Some emerging evidence on the effects of inflammation and metabolic abnormalities on the brain can possibly explain this association. For example, treatment with IL-1β, a pro-inflammatory cytokine shown to be increased in patients with depression or with schizophrenia, decreases neurogenesis in human hippocampal progenitor cells (Zunszain et al., 2012). Further evidence of the effect of metabolism on the brain comes from resting-state studies. A study from Doucet and colleagues (2018) investigated the correlation between BMI and the functional organization of resting-state brain networks, such as the default mode network (DMN), and the Sensory Motor Network (SMN). They found a positive correlation between BMI and connectivity between the DMN, the SMN and other cerebral networks. Such increased integration between networks suggests an increase of sensory driven behavior in subjects with higher BMI (Doucet et al., 2018). More interestingly, FEP patients show similar connectivity alterations. Resting-state studies have found that the early stage of schizophrenia is

associated with increased connectivity between fronto-parietal networks involved in the control of cognitive and sensory functions (Anhoj et al., 2018).

Finally, obesity and overweight are associated with brain structural abnormalities (frontal and temporal grey matter atrophy and reduced integrity of white matter in the corpus callosum) and poor cognitive and functional outcomes, typically present in FEP (Minichino et al., 2017).

Growing evidence suggests increased levels of peripheral immune markers in patients at the onset of psychosis (Di Nicola et al., 2013; Hepgul et al., 2012; Mondelli et al., 2015; Zajkowska and Mondelli, 2014), and the potential for biomarkers of inflammation as predictors of long-term illness course (Mondelli et al., 2015). Similarly, levels of the acute phase inflammatory marker C-reactive protein (CRP) have been found moderately increased in patients with schizophrenia (Wang et al., 2017) and resulted to be correlated with the severity of illness and with the presence of relapses (Orsolini et al., 2018). Furthermore, in both chronic schizophrenia and at the onset of psychosis, CRP blood levels have been correlated with cognitive and negative symptoms severity (Baumeister et al., 2014). Despite such evidence, longitudinal studies investigating CRP as a predictor of clinical outcome at the onset of psychosis are currently lacking.

A further aspect to consider is that, due to the relationship between the immune and the metabolic system, high levels of peripheral inflammation are generally associated with metabolic abnormalities in both the general population and in FEP patients (Russell et al., 2015) (Petrikis et al., 2015; Pillinger et al., 2017a; Pillinger et al., 2017b; S et al., 2013). More interestingly, weight gain, increased visceral fat and impaired glucose metabolism have been detected also in drug naïve patients (Correll et al., 2014), with altered insulin signaling being present also in unaffected siblings (Chouinard et al., 2018). This suggests these abnormalities to be partly independent of treatment exposure and rather to be linked to innate mechanisms of psychiatric illness, including a chronic inflammation state.

All this evidence supports the relevance of considering an overall metabolic-inflammatory status when looking for biomarkers of clinical outcomes of psychosis. No study so far has tested the impact of the combination of inflammation-weight gain-metabolic abnormalities on the clinical outcome of FEP patients. Based on this evidence, this study aimed to investigate whether, in a sample of FEP

patients, inflammation and metabolic status could be considered together as part of an overall inflammatory-metabolic factor associated with clinical symptoms at baseline and at 1-year follow-up clinical outcome. There is a compelling body of evidence on the association between inflammation and BMI and adiposity. In fact, obese individuals present higher circulating levels of CRP (Firdous 2014); in particular, it is now acknowledged that adipose tissue can contribute to increased peripheral inflammation due to the increased release of cytokines from adipocytes and infiltrated macrophages (Wensveen et al., 2015).

As a consequence, we hypothesized that a single factor representing a latent metabolic process variable between individuals would express a linear combination of baseline inflammation, BMI and/or adiposity and that it could be positively associated with symptoms severity at baseline and with 1-year follow-up symptoms severity and treatment response.

2. Materials and Methods

This is a naturalistic longitudinal study in which FEP patients were assessed at baseline (i.e., as soon as possible and within 3 months after the first contact with psychiatric services) and then were followed-up prospectively for their clinical outcome at 1 year.

2.1 Sample and study design

First Episode Psychosis Patients

Fifty-one first episode psychosis patients were recruited in South-East London as part of the Physical health and substance Use Measures in first onset Psychosis (PUMP) and Genetics and Psychosis (GAP) studies. The recruitment strategy was based on contacting inpatient and outpatient units of the South London and Maudsley (SLAM) NHS Foundation Trust, interviewing staff and reviewing clinical notes, and approaching all subjects aged 18–65 who presented for the first time to these services for a functional psychotic illness. Patients not fluent in English, with organic psychosis, learning disabilities, mental retardation, and physical comorbidities affecting the immune system (acute and chronic infections, auto-immune disorders, diabetes and cardiovascular disorders) were excluded from the study. Two patients were not included as they had an acute infection and a history of chronic inflammation due to an autoimmune disorder, respectively; seven patients with diabetes, of which six were on insulin treatment, were also excluded. The final sample was of 42 FEP patients. All patients were assessed as soon as possible after their first contact with psychiatric services, and not later than 3 months from the first contact. After 1 year, a clinical follow-up was completed on all patients to establish treatment response and illness course. The study was approved by the local Research Ethics Committee, in accordance with the code of ethics of the World Medical Association, and written informed consent was obtained from all participants.

At the time of the first assessment, 20 patients were taking olanzapine, 13 were taking risperidone,

4 were taking quetiapine, 3 were taking aripiprazole, 1 was taking haloperidol and 1 was taking zuclopenthixole. Total duration of treatment from baseline (T1) to follow-up (T2) was calculated, as well as total treatment duration at T1 and the main duration of untreated psychosis. Unfortunately, information about the main duration of untreated psychosis was available for 34 patients only. According to published guidelines (Gardner et al., 2010), chlorpromazine equivalents of the cumulative dosage of medications at T1 and T2 were calculated.

Twenty-one patients received a DSM-IV diagnosis of schizophrenia/schizophreniform disorder, 17 of schizoaffective or affective psychosis and 4 of psychotic disorder not otherwise specified. Validation of clinical diagnosis was obtained using the Operational Criteria (OPCRIT+), reviewing the case notes in the first month following first contact with services. All diagnoses were performed by qualified psychiatrists, subject to comprehensive training and inter-rater reliability testing ($\kappa = 0.9$). Indication of clinical status and severity of psychotic symptoms were derived both at baseline (T1) and at 1-year follow-up (T2), from the Positive and Negative Syndrome Scale (PANSS).

PANSS total score was calculated at T2 and was used as a measure of clinical outcome at follow-up. Positive, Negative and Global symptoms PANSS subscales were used to measure symptoms domains at follow-up. We also calculated a continuous measure of treatment response, in terms of percentage of improvement from baseline. This was estimated as change in PANSS total scores from baseline to follow-up, taking into account PANSS total scores and subtracting a score of 30, as even individuals without any mental health condition could score 30 in the PANSS. Therefore, as described in previous articles (Leucht et al., 2007), we used the following formula: 100 x ((baseline PANSS total score-30)- follow-up PANSS total score-30)/baseline PANSS total score-30).

Healthy controls

In order to compare T1 metabolic status of our clinical sample with that of general population, 50 healthy controls (HC) were recruited in South-East London at T1 through advertisement in local newspapers, hospitals, and job centres, as well as from existing volunteer databases. Participants

not fluent in English, with learning disabilities, mental retardation, any diagnosis of present or past mental disorders and physical disorders affecting the immune system (acute and chronic infections, auto-immune disorders, diabetes and cardiovascular disorders) were excluded from the study. Controls were screened using the Psychosis Screening Questionnaire (Bebbington and Nayani, 1995). One participant with diabetes, one with a history of cardiovascular disorders and 2 with autoimmune disorders were excluded from the study. The final sample size was 46. Socio-demographic data and metabolic parameters were collected with the same procedure used for patients. Unfortunately, data on T1 fasting glucose were not available in healthy controls.

After testing normality for metabolic variables (see 2.3), for normally distributed ones, namely Hb1Ac, Cholesterol and LDL, independent t-tests were used to assess differences between patients and controls. Instead, Mann-Whitney U-tests were performed to explore differences in BMI, hsCRP and TG.

2.2 Inflammation and metabolic markers

Weight was measured to the nearest 0.1 kg, wearing minimal clothing, with an analogue floor scale. Height was measured to the nearest 5 mm, without shoes and using a measuring tape. BMI was then calculated: body weight (kg)/square of height (m^2).

Fasting blood samples were taken in all subjects only at baseline (T1). Although time of collection varied for each participant, all samples were taken in the morning. High sensitivity C-reactive protein (hsCRP) was used to assess inflammation and analyzed from serum samples using the Cormay hsCRP assay (Hepgul et al., 2012), (laboratory reference range: low <0.1 mg/L; average 1.0-3.0 mg/L; high>3.0 mg/L). Serum total cholesterol and triglycerides (TG) were measured in serum at the time of the blood draw using an enzymatic assay. Low-density lipoprotein (LDL) cholesterol was then subsequently calculated using the Friedewald equation (see Hepgul et al., 2012). Glycated hemoglobin (HbA1c) was measured in plasma at the time of the blood draw using the Premier

Hb9210 system, employing principles of boronate affinity and high-performance liquid chromatography. Plasma glucose was measured in plasma upon arrival to the lab using the ADVIA 2400 to analyze a hexokinase assay (intra-assay CV=0.55, inter-assay CV =2.8). Sociodemographic characteristics, clinical measures at T1 and T2 and levels of biomarkers of the sample at T1 are shown in Table 1.

2.3 Data analysis

Data were analyzed using the Statistical Package for Social Sciences, version 24.0 (SPSS Inc., USA). Continuous variables are presented as mean values with their standard deviations in Table 1. Boxplots of metabolic biomarkers were generated to identify possible outliers for each separate biomarker. The identified outliers (>1.5 interquartile range) were removed before running the statistical analyses if a specific reason for their outlier status was identified, that is, chronic and acute diseases affecting inflammation and metabolism. As participants with such comorbidities were all removed a priori from the sample, there were no outliers to remove.

2.3.1 Factor analyses

Seven metabolic/inflammatory variables (hsCRP, BMI, Hb1Ac, fasting glucose, triglycerides, cholesterol and LDL) at baseline were entered into a factor analysis model (Principal Component Analysis-PCA) using SPSS, version 24. PCA allows to combine several variables in a smaller number of factors: those variables that strongly correlate with each other are gathered in one factor accounting for all of them. As variables were measured with different units, and as some of them were not normally distributed, a rank based inverse normal transformation with Blom method was applied to all of them before entering the model.

The Kaiser-Meyer-Oklin (KMO) test and the Bartlett spherical test were used as preliminary tests for factor analysis. Due to our preliminary hypothesis that inflammation, BMI and/or adiposity could be highly correlated with each other and also be positively associated with T1 and T2 symptoms severity and with T2 treatment response, we set the number of factors to 3:1 factor expressing relationship between inflammation and BMI, 1 factor for lipid profile and 1 factor for glycemic profile. In order to choose the best rotation method (oblique or orthogonal), Direct Oblimin rotation was preliminary chosen to explore the correlation matrix between factors. The resulting correlation matrix between

factor 1 and 3 showed a value above 0.32 (0.327), so we opted for a Direct Oblimin oblique method (Corner, 2009).

Notably, a factoring of these metabolic variables with PCA has never been used previously. Moreover, we could not test the same factoring in another sample, to confirm that variables clustered in the same way. So, we investigated whether, beside the correlations between variables in these specific samples, the same results could be found simply using the mean of metabolic variables z scores, grouped according to our hypothesis. This is simply a measure of the deviation of each patient from population mean. To test this, we calculated the mean of z scores of hsCRP, BMI and TG for factor 1, that of Cholesterol and LDL for factor 2 and that of HbA1c and fasting glucose for factor 3. Then, we correlated the resulting factors with T1 and T2 clinical variables.

In order to control for T2 metabolic variables effect on T2 symptoms, we conducted a PCA and we calculated T2 metabolic factors (data were available for 39 patients). Moreover, we calculated BMI, hsCRP and TG T1-T2 trajectory of change. We then performed a correlation analysis between T2 metabolic factors and T2 clinical variables and between BMI, hsCRP and TG trajectory of change and T2 clinical variables.

2.3.3 Statistical correlations and regressions between baseline factors and clinical outcome

Correlation analyses between metabolic factors at T1 and clinical measures at T1 and T2 were explored. Then, for those metabolic factors that resulted to be correlated with T2 variables, a linear regression analysis was performed to explore whether metabolic factors were associated with T2 outcome variables [T2 Treatment response, PANSS total score, PANSS negative score, PANSS, positive score, PANSS global score].

Before running regression analyses, we explored the association of T1 and T2 medication, socio-demographic variables, namely gender, ethnicity and age, with metabolic factors resulting from PCA, as well as with T1 and T2 clinical measures. We also controlled for any difference in clinical and

metabolic variables between patients prescribed with olanzapine at T1 and those who were on other medication. This is because of the well-known ability of olanzapine to affect metabolism (Park et al., 2013).

Moreover, as tobacco-smoking, cannabis and alcohol consumption are well-known to act both on inflammatory and metabolic conditions (Fond et al., 2017), we tested whether these three variables affected metabolic factors and clinical variables. Data on lifetime use (yes-no) of tobacco and alcohol were available for 41 FEP and 45 HC, while data on lifetime cannabis use were available for all participants (Table 1).

Pearson's correlations and linear regressions were performed with bootstrapping method. This is a statistical approach that relies on random resampling with replacement (number of resamplings in our analyses: 5000) and allows assigning measures of accuracy to sample estimates. As clinical variables showed a skewed distribution, bootstrapping allowed performing the statistic test eliminating possible confounding effects of variable distribution. Each regression model was also corrected for baseline symptoms to test if the association between metabolic factors and follow-up clinical variables could be mediated by baseline clinical variables.

A Bonferroni correction was adopted with $\alpha = 0.0125$ for correlations between metabolic factors and T1 symptomatic domains (0.05/4, as we had 4 dependent variables: three T1 PANSS sub scores and T1 PANSS total score); $\alpha = 0.01$ for linear regressions between T1 metabolic factors and T2 symptomatic domains (0.05/5 as there were 5 dependent variables: three T2 PANSS sub scores, T2 PANSS total score and T2 treatment response).

3. Results

3.1 FEP vs HC

HC group was matched with the FEP group for sociodemographic variables (Table 1). The sex rate (M/F) was 26/16 in the FEP sample and 22/24 in the sample of HC. Ethnicities in the FEP sample were: 12 white British, 8 white Caucasian, 4 Asian, 9 black Caribbean, 8 black African, 1 black other; ethnicities in the healthy controls sample were the following: 16 white British, 4 white Caucasian, 3 mixed race, 3 Asian, 10 black Caribbean, 9 black African, 1 black other).

FEP showed higher HbA1c ($t=2.15$, $p=0.034$), TG (Mann Whitney $U=726.5$, $p=0.045$) and BMI (Mann Whitney $U=700.0$ $p=0.026$) than HC at baseline. There was a trend difference in hsCRP with patients showing higher levels of hsCRP compared with controls (Mann Whitney $U= 739.5$, $p=0.057$) (See Table 1).

FEP smoked both tobacco ($X^2=6.4$, $p=0.04$) and cannabis ($X^2=4.8$, $p=0.028$) more than HC (Table 1), while no difference was found in alcohol consumption (see table 1). Interestingly, the majority of patients smoked and drunk alcohol (Table 1).

In the FEP sample, the mean duration of antipsychotic treatment from T1 to T2 was 222.2 ± 161.4 days, the mean duration of treatment at T1 was 41.4 ± 45.1 days, while the main duration of untreated psychosis was 59.76 ± 182.8 days. The cumulative dose of antipsychotic treatment received at T1 was $17.2\times10^3 \pm 26.4\times10^3$ mg, while the cumulative dose of antipsychotic treatment at the time of follow-up assessment was $10.5\times10^5 \pm 8.8\times10^5$ mg.

3.2 Factor analysis

The KMO test (0.614) and the Bartlett test (Chi = 110.8, $p <0.001$) indicated that the correlation matrix between metabolic items was adequate for performing a PCA. PCA allowed identifying 3 factors contributing to 36.9%, 28.8% and 12.6% of the explained variance respectively (cumulative variance =79%). Each factor corresponded to a different metabolic domain. Considering metabolic items with the highest score within each factor, the hsCRP clustered with triglycerides and BMI in

factor 1; cholesterol and LDL clustered together in factor 2 and fasting glucose and HbA1c clustered in factor 3 (Table 2). Extraction communalities were all above 0.6. Extraction communalities are estimates of the variance in each variable accounted for by the components, so high values of communalities mean that the resulting components represent all variables well.

T2 metabolic variables clustered in three factors (KMO test=0.544; Bartlett test: Chi = 79.1, p <0.001). Factor loadings were similar to those of T1 metabolic factors. Factor 1 (T2 hsCRP+T2TG+T2BMI) explained 38,7% of the variance, T2 factor 2 (T2 LDL+T2 Chol) explained 20% of total variance, and factor 3 (T2 HbA1c+T2 fasting glucose) explained 14.7% of the variance. The mean T1-T2 trajectory of change was 1.9 ± 5.7, 1.03 ± 4.2 and -0.05 ± 0.7 for hsCRP, BMI and TG respectively.

3.3 Correlation analyses

Bootstrapped Pearson's correlation analysis between metabolic factors and clinical measures at T1 revealed a significant positive association between metabolic factor 1 and T1 PANSS negative score (r=0.354, p=0.021). When correlation between metabolic factors and T2 clinical measures were explored, we found that factor 1 positively correlated with T2 PANSS total score (r=0.499, p=0.001), T2 PANSS positive score (r=0.356, p=0.021), T2 PANSS negative score (r=0.352, p=0.022,) and T2 PANSS global score (r=0.516, p<0.001). A significant negative association of both factor 1 and factor 2 with 1-year T2 treatment response was also found (r=-0.771, p=0.014 and r=-0.327, p=0.034, respectively). Correlation analysis between factor 3 and clinical variables at T1 and T2 showed no significant results (all p>0.05).

Confirming that these results persist independently of how the single variables are associated with each other in this sample, Pearson's correlations with bootstrapping using the same metabolic factors calculated as means of z scores revealed overlapping results. We confirmed a positive association between metabolic factor 1 and T1 PANSS negative score (r=0.368, p=0.017,) and with T2 PANSS total score (r=0.496, p=0.001), T2 PANSS positive score (r=0.339, p=0.0278), T2 PANSS

negative score (r=0.356, p=0.021) and T2 PANSS global score (r=0.520, p<0.001,). Also, the negative association of factor 1 and factor 2 with 1-year T2 treatment response was confirmed (r=-0.367, p=0.017, and r=-0.336, p=0.030, respectively). Finally, no significant correlations were found between factor 3 and clinical variables, again. Gender and ethnicity were not associated with any T1 and T2 variable (all bootstrapped p>0.05). Although age was not correlated with any clinical variable, a significant Pearson's correlation was found between age and metabolic factor 1 (r=0.371, bootstrapped p<0.015). In order to investigate the effect of age, this variable was added to multiple regression models. As it was not associated with dependent variables, there was no risk of collinearity (this was verified by SPSS collinearity diagnostics).

While alcohol and tobacco showed no effect on metabolic factors and clinical variables (Mann-Whitney, all p > 0.05), cannabis use was positively associated with T2 positive symptoms (Mann-Whitney U=72000, p=0.018). Therefore, we ran an additional regression model including cannabis as factor for T2 positive PANSS score.

Equivalents of chlorpromazine at T1 and T2, total duration of medication at T1 and from T1 to T2 and duration of untreated psychosis showed no effect on both metabolic factors and T1 and T2 clinical variables, therefore, these variables were excluded from multiple regression models (all bootstrapped p>0.05). Patients on olanzapine resulted to have higher values of metabolic factor 1 (t=-2.4, p=0.02). So, after running all regression models, we tried to add olanzapine treatment as a variable to test whether this significantly affected results.

Finally, when we explored correlation between T2 metabolic factors and T2 clinical variables, we found a significant association of T2 metabolic factor 1 with T2 PANSS negative scores (r=0.407, p=0.015) and T2 total PANSS (R=0.355, P=0.036), but not with other symptoms categories. Similarly, we found that only hsCRP trajectory of change (but not BMI) correlated with T2 PANSS negative score (r=0.432, p=0.010). This was probably driven by the association between hsCrp and T2 PANSS negative score (r=0.399, p=0.018).

3.4 Regression analyses with Metabolic factor 1 (hsCRP, TG, BMI) corrected for age

The following regression analysis, corrected for age, confirmed that metabolic factor 1 predicted T2 global PANSS scores (R^2=0.350, bootstrapped p<0.001, See Table 3). T1 global scores were not added to the model as they were not correlated with T2 global symptoms scores (Pearson's bootstrapped correlation: r=0.111, p=0.480).

Metabolic factor 1 alone also predicted T2 PANSS total score (R^2=0.249, p=0.001), T2 PANSS positive score (R^2=0.127, p=0.009) and T2 PANSS negative score (R^2=0.124, p=0.007). When these models were corrected for T1 symptoms scores, metabolic factor 1 was still predictive of T2 PANSS total score (total R^2=0.380, bootstrapped p=0.001, see multiple regression model in Table 4).

When the association with T2 positive symptoms severity was explored, metabolic factor 1 showed a substantial contribution to the model, surviving correction for T1 positive symptoms scores and for cannabis use (total R^2=0.415, metabolic factor 1 bootstrapped p=0.004, β=0.616 vs T1 symptoms bootstrapped p=0.057, β=0.187 and cannabis use bootstrapped p=0.041, β=-0.121, Table 5). Finally, metabolic factor 1 contribution to the predictive model of T2 negative symptoms did not survive correction for multiple comparisons (factor 1 bootstrapped p=0.031, β=0.259 vs T1 negative symptoms score bootstrapped p=0.083, β=0.351) (Table 6).

Metabolic factor 1 (hsCRP, TC, BMI) and 2 (Cholesterol and LDL) and Treatment Response, corrected for age.

Regression analysis revealed that, when including both metabolic factor 1 and 2 into the same model, metabolic factor 1 was more predictive of T2 treatment response (total R^2=0.274; factor 1 bootstrapped p=0.007 vs factor 2 bootstrapped p=0.037, Table 7). Notably, after adding olanzapine treatment as a variable in all regression models, metabolic factor 1 still predicted clinical variables at T2 (PANSS T2 global score: p=0.001, β=0.675; PANSS T2 Total score: p=0.002, β=0.616; PANSS T2 positive score: p=0.005, β=0.450; PANSS T2 negative score: p=0.018, β=0.350; Treatment

response: p=0.010, β=-0.472), suggesting that the effect was not confounded by the effect of olanzapine treatment.

Discussion

In this longitudinal study in first episode psychosis patients, we found that those with worse inflammatory-metabolic status at baseline, defined as higher levels of hsCRP, BMI and triglycerides, had worse clinical outcome at 1-year follow-up as demonstrated by the presence of higher PANSS scores and reduced rate of treatment response at 1-year follow-up.

The baseline levels of metabolic and inflammatory markers of our patients reflected and confirmed the presence of subtle metabolic/inflammatory abnormalities in the early stages of psychosis, where higher levels of BMI, CRP and triglycerides have been already previously described (Hepgul et al., 2012; Misiak et al., 2017; Pillinger et al., 2017b).

We would have expected a gender-driven difference in terms of CRP levels in the FEP sample. Previous studies exploring relationship between C-reactive protein and psychiatric disorders have found the correlation between CRP and depressive symptoms to be present only in depressed men (Tayefi et al., 2017) (Vetter et al., 2013), who showed higher CRP values than women. By contrast, a study on 88 patients with schizophrenia (40% males) found that higher hsCRP levels in patients were associated with female gender, (Joseph et al., 2015). Moreover, another study on 485 patients with schizophrenia (50% males) from Wysokinski and colleagues found that the rate of patients having CRP above 3 mg/L (with higher risk of cardiovascular problem) was higher in women (Wysokinski et al., 2015).

The reason we did not find a difference in CRP similar to that of studies on schizophrenia may be attributed to the smaller sample size, to the different sex ratio and to the larger diagnostic spectrum of our sample, including patients with schizophrenia, schizoaffective disorder and affective psychosis.

The factor analysis showed that the inflammatory marker CRP clustered into a factor with BMI and triglycerides at baseline, as we expected and as confirmed by the alternative method with z-scores

mean. This is in line with findings in the general population (Ellulu et al., 2017) and highlights a close association between inflammation, body weight and eating habits (as triglycerides levels are mainly influenced by diet) in FEP patients. Interestingly, baseline triglycerides have been found associated with later symptom severity and poor functioning in patients with schizophrenia in a 5-year follow-up longitudinal study (Solberg et al., 2016). This seems to support the role of triglycerides levels as potential predictor of clinical state together with inflammation. Furthermore, this evidence suggests that FEP patients could benefit from a dietary education aiming to reduce triglycerides levels. For example, it has been shown that a controlled quality and quantity of food intake, low alcohol consumption (AbouRjaili et al., 2010) and a high-omega-3 fatty acids diet (Shearer et al., 2012) are able to significantly reduce triglycerides levels in the general population.

Factor 1 was associated with baseline PANSS negative symptoms. Although this result ($p=0.021$) did not survive correction for multiple comparisons ($\alpha = 0.0125$), it is consistent with previous studies showing higher CRP levels in patients with negative symptoms. This result is also consistent with increased weight gain in the same category of patients, as they typically show sedentary life and physical inactivity. Finally, this should be taken into account when interpreting results on factor 1 ability to predict T2 negative symptoms (which did not survive correction as well), as collinearity between factor 1 and T1 negative symptoms score affected the model. Furthermore, also results from correlations between T2 metabolic factors and T2 clinical variables proved that the current overall metabolic-inflammatory status is associated with current negative symptoms, but not with other symptoms clusters and with treatment response. Hence, the ability of baseline metabolic factors to predict later positive symptoms, treatment response and general psychopathology offer an important opportunity of early intervention in these patients.

The most interesting and novel finding is the role of factor 1 in predicting PANSS positive score, PANSS global score, PANSS total score and treatment response rate at 1-year follow-up. This could possibly suggest an effect of abnormal metabolic and inflammatory status on the brain. A recent study has highlighted that weight gain is associated with brain structural abnormalities such as reduced grey matter integrity in the temporal lobe (Minichino et al., 2017). Interestingly, the same

brain region has been implicated in the genesis of positive symptoms of psychosis (Fusar-Poli et al., 2012) and grey matter reduction of the superior temporal gyrus has been found during transition to psychosis (Takahashi et al., 2009). More interestingly, in our sample a predictive model of positive symptoms severity included the metabolic-inflammatory status together with cannabis use. There is vast evidence of the association between cannabis consumption and the development of schizophrenia (Arseneault et al., 2004). However, in light of our results, future studies should investigate the interaction between inflammation, metabolism and cannabis use and its effect on positive dimension of schizophrenia.

Metabolic factor 1 implication with PANSS global scale may be attributed to the well-known relationship between inflammation and cognitive-affective symptoms (Baumeister et al., 2014). Peripheral inflammation may affect the brain, possibly through cytokines passing the blood brain barrier and triggering microglia activation (Cattaneo et al., 2015) and ultimately affecting synaptic pruning and brain function and connectivity (Cannon, 2016). Factor 1 was also predictive of follow-up treatment response and this suggests that new strategies of intervention may target the inflammatory and metabolic status at early stages of psychosis in order to reduce possible effects of abnormal metabolic-inflammatory status on the brain. Although factor 2 was less predictive of treatment response, the role of diet-unrelated lipids such as LDL and total cholesterol should be more fully investigated in future studies.

Finally, the cumulative dose of antipsychotics, in terms of baseline and follow-up chlorpromazine equivalents, had no effect on metabolic and clinical variables. One possible explanation may be that treatment response and symptoms severity in this specific sample were not correlated with antipsychotics dosage. Also, olanzapine treatment, known to affect metabolism, did not affect our results significantly. This suggests that a latent metabolic factor, linking inflammation and metabolic status and possibly independent from medication, may contribute to the pathophysiology of psychosis.

The identification of a key predictive factor including interdependent immune and metabolic variables in FEP, supports the potential for evaluating a number of strategies of early intervention, including physical exercise, diet monitoring and anti-inflammatory treatment for patients with a specifically abnormal metabolic-inflammatory status. Lifestyle interventions and a more careful choice of type and timing of antipsychotic prescription would possibly help a better control of the metabolic/inflammatory status and contribute to better clinical outcomes. Indeed, FEP patients may not only benefit from a dietary education, but also from physical exercise, that could help preventing weight gain. In fact, a study from Gates and colleagues (2015) pointed out that prevention of weight gain is much more achievable and long-lasting than weight loss in FEP patients. The same authors highlight the importance of early intervention for smoking cessation, that is also likely to result in improved health outcomes and, more specifically, in reduced inflammation. Although patients with a first episode of psychosis are six times more likely to be current tobacco users than age-matched and sex-matched healthy controls (as confirmed by our results), people with schizophrenia who quit early are likely to maintain their smoking cessation status (Gates et al., 2015).

As later interventions, anti-inflammatory medications (Mondelli et al., 2017) may reverse microglia activation and improve functioning and cognition.

We need to acknowledge few limitations of this study. First, the sample size of our FEP patients was relatively small and our factor analysis needs to be replicated in a larger sample. Second, we did not have specific measures of insulin resistance, adiposity or adipose distribution that could possibly further refine the characterization of a metabolic-inflammatory factor; and these factors should be explored in future studies. Finally, 17 patients were on antidepressants, but we were not able to control for the effect of depressive symptoms and anti-depressant medication on patients' metabolic-inflammatory status. This is something that future studies should try to address.

Conclusions

In conclusion, our findings further confirm a close interdependency between inflammation and metabolism in patients at their onset of psychosis as already partly suggested by our previous studies (Hepgul et al., 2012; Russell et al., 2015). Our data also support the hypothesis that these physical health factors may play a role in the clinical course of psychosis and that the metabolic-inflammatory status should be taken into account in early intervention approaches for psychosis. Such approaches may include a dietary education, physical exercise and early intervention for smoking cessation.

Contributors

All authors have materially participated in the research and/or article preparation. All authors have approved the final article.

Authorship

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Conflicts of interest

The authors have no conflicts to disclose.

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Conflicts of interest

The authors have no conflicts to disclose.

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Table 1 *Sociodemographic characteristics, baseline levels of biomarkers and clinical variables indicated as mean ± standard deviation. Significant tests (p<0.05) are in bold.*

	FEP (=42)	**HC (n=46)**	**Test and significance**
Age (y)	30.3±9.8	28.7±9.2	U=859.5, p=0.373
Gender (M/F)	26/17	22/28	X^2=2.5, p=0.113
Ethnicity (White/Black/Asian/Mixed)	20/18/4	20/20/3/3	X^2=8.7, p=0.560
T1 [1]hsCRP (mg/L)	2.3±3.2	1.5±1.9	U=739.5, p=0.057
T1 [2]HbA1c (%)	5.3±0.4	5.1±0.3	t=2.15, **p=0.034**
T1 Fasting glucose (mmol/L)	4.7±0.4	-	-
T1 [3]Triglycerides (mg/dl)	1.4±0.7	1.1±0.5	U=726.5, **p=0.045**
T1 [4]Cholesterol (mg/dl)	4.9±0.7	5.1±1.1	t=1.2, p=0.237
T1 [5]LDL (mg/dl)	2.8±0.6	3.05±0.90	t=1.3, p=0.210
T1 BMI kg/m^2	26.9±5.2	24.4±3.4	U=700.0, **p=0.026**
Tobacco lifetime use (yes/no)	34/7 **(n=41)**	26/19 **(n=45)**	X^2=6.4, **p=0.04**
Alcohol lifetime use (yes/no)	37/4 **(n=41)**	43/2 **(n=45)**	X^2=0.93, p=0.63
Cannabis lifetime use (yes/no	33/9	26/20	X^2=4.8, p**=0.028**
T1 [6]PANSS total score **T2 PANSS total score**	59.4±12.3 50.1±15.2	-	-
T1 PANSS positive score **T2 PANSS positive score**	12.8±4.9 11.9±5.5	-	-
T1 PANSS negative score **T2 PANSS negative score**	15.1±5.9 13.1±5.9	-	-
T1 PANSS global score **T2 PANSS global score**	28.7±5.9 24.1±6.9	-	-
Treatment response	27.5±56.3	-	-

1 High sensitivity C reactive protein
2 Glycated hemoglobine
3 Triglycerides
4 Total cholesterol
5 Low Density Lipoprotein cholesterol
6 Positive and Negative Syndrome Scale

Table 2 *Metabolic variables Principal component analysis Structure after Direct Oblimin rotation.*

The bold values indicate the items highest scores for each factor.

Structure Matrix

	Components		
	1 variance explained: 36.9% eigenvalue: 2.5	**2** variance explained: 28.8% eigenvalue: 2.0	**3** variance explained:12.6% eigenvalue: 0.8
Normal score of T1 [1]hsCRP	**0.829**	-0.010	0.463
Normal score of T1 [2]HbA1c	0.228	-0.076	**0.915**
Normal Score of T1 fasting glucose	0.442	-0.262	**0.820**
Normal score of T1 [3]TG	**0.744**	0.433	0.296
Normal score of T1 [4]Cholesterol	0.209	**0.940**	-0.099
Normal score of T1 [5]LDL	0.121	**0.937**	-0.186
Normal score of T1 BMI	**0.831**	0.156	0.149

Extraction method: Principal component analysis
Rotation method: Oblimin with Kaiser Normalization

1 High sensitivity C reactive protein
2 Glycated hemoglobine
3 Triglycerides
4Total cholesterol
5 Low Density Lipoprotein cholesterol

Table 3 Linear regression analysis with bootstrapping with independent variable: metabolic factor 1. Dependent variable: T2 global PANSS score. Covariate: age.

T2 [1]PANSS global score							
Regression model				Variable(s) included	Predictors (Bootstrapping)		
	R	R^2	p-value		*B(SE)*	β	*p-value*
Forced entry, multiple							
T1 Metabolic factor 1 ([2]hsCRP+[3]TG+BMI)	0.592	0.350	<0.001	T1 Metabolic factor 1 (hsCRP+TG+BMI)	-4.4(0.9)	0.632	<0.001
Age				Age	-0.2(0.1)	-0.312	0.750

1Positive and Negative Syndrome Scale
2 High sensitivity C reactive protein
3Triglycerides

Table 4 Linear regression analysis with bootstrapping with independent variables: metabolic factor 1 and T1 total PANSS score. Dependent variable: T2 total PANSS score. Covariate: age.

The linear model illustrates the single contribution of each independent variable in predicting the dependent one. In the multiple model independent variables are considered together.

T2 [1]PANSS total score							
Regression model				Variable(s) included	Predictors (Bootstrapping)		
	R	R^2	p-value		*B(SE)*	β	*p-value*
Linear							
T1 Metabolic factor 1 ([2]hsCRP+[3]TG+BMI)	0.499	0.249	0.001	T1 Metabolic factor 1 (hsCRP+TG+BMI)	7.5(1.6)	0.499	<0.001
T1 PANSS total score	0.308	0.095	0.047	T1 PANSS total score	0.4(0.2)	0.308	0.022
Forced entry, multiple							
T1 Metabolic factor 1 (hsCRP+TG+BMI)	0.617	0.380	<0.001	T1 Metabolic factor 1 (hsCRP+TG+BMI)	8.8(2.0)	0.581	0.001
T1 PANSS total score				T1 PANSS total score	0.2(0.2)	0.183	0.167
Age					-0.5(0.2)	-0.313	0.032

1Positive and Negative Syndrome Scale
2 High sensitivity C reactive protein
3Triglycerides

Table 5 Linear regression analysis with bootstrapping with independent variables: metabolic factor 1 and T1 PANSS positive score. Dependent variable: T2 positive PANSS score. Covariates: age, cannabis lifetime use. *The linear model illustrates the single contribution of each independent variable in predicting the dependent one. In the multiple model independent variables are considered together.*

T2 [1]PANSS positive score							
Regression model				Variable(s) included	Predictors (Bootstrapping)		
	R	R^2	p-value		*B(SE)*	*β*	*p-value*
Linear							
T1 Metabolic factor 1 ([2]hsCRP+[3]TG+BMI)	0.356	0.127	0.021	T1 Metabolic factor 1 (hsCRP+TG+BMI)	1.9(0.6)	0.356	0.009
T1 PANSS positive score	0.401	0.161	0.009	T1 PANSS positive score	0.4(0.2)	0.401	0.024
Cannabis lifetime use (yes/no)	0.347	0.121	0.024	Cannabis lifetime use (yes/no)	4.6(1.02)	0.307	0.003
Forced entry, multiple							
T1 Metabolic factor 1 (hsCRP+TG+BMI)	0.644	0.415	<0.001	T1 Metabolic factor 1 (hsCRP+TG+BMI)	9.3(1.2)	0.616	0.004
T1 PANSS positive score				T1 PANSS positive score	0.2(0.2)	0.187	0.057
Age				Age	-0.5(0.3)	-0.182	0.049
Cannabis lifetime use (yes/no)				Cannabis (yes/no)	-3.6(4.1)	-0.121.	0.041

1Positive and Negative Syndrome Scale
2 High sensitivity C reactive protein
3Triglycerides

Table 6 Linear regression analysis with bootstrapping with independent variables: metabolic factor 1 and T1 PANSS negative score. Dependent variable: T2 PANSS negative score. Covariate: age. *The linear model illustrates the single contribution of each independent variable in predicting the dependent one. In the multiple model independent variables are considered together.*

T2 [1]PANSS negative score							
Regression model				Variable(s) included	Predictors (Bootstrapping)		
	R	R^2	p-value		*B(SE)*	*β*	*p-value*
Linear							
T1 Metabolic factor 1 ([2]hsCRP+[3]TG+BMI)	0.352	0.124	0.022	T1 Metabolic factor 1 (CRP+TG+BMI)	2.1(0.6)	0.352	0.007
T1 PANSS negative score	0.423	0.179	0.005	T1 PANSS negative score	0.4(0.2)	0.423	0.012
Forced entry, multiple							
T1 Metabolic factor 1 (CRP+TG+BMI) **T1 PANSS negative score** **Age**	0.495	0.245	0.013	T1 Metabolic factor 1 (CRP+TG+BMI) T1 PANSS negative score Age	1.7(0.8) 0.3(0.2) -0.06(0.1)	0.295 0.351 -0.351	0.031 0.083 0.199

1Positive and Negative Syndrome Scale
2 High sensitivity C reactive protein
3Triglycerides

Table 7. Linear regression analysis with bootstrapping with independent variables: metabolic factor 1 and metabolic factor 2. Dependent variable: T2 treatment response. Covariate: age.

The linear model illustrates the single contribution of each independent variable in predicting the dependent one. In the multiple model independent variables are considered together.

Treatment Response							
Regression model				Variable(s) included	Predictors (Bootstrapping)		
	R	R^2	p-value		*B(SE)*	β	*p-value*
Linear							
T1 Metabolic factor 1 ([1]hsCRP+[2]TG+BMI)	0.377	0.142	0.014	T1 Metabolic factor 1 (hsCRP+TG+BMI)	-21.2(7.9)	-0.38	0.011
T1 Metabolic factor 2 ([3]Chol+[4]LDL)	0.327	0.107	0.034	T1 Metabolic factor 2 (Chol+LDL)	-18.4(7.2)	-0.33	0.015
Forced entry, multiple							
T1 Metabolic factor 1 (hsCRP+TG+BMI) **T1 Metabolic factor 2 (Chol+LDL)** **Age**	0.523	0.274	0.006	T1 Metabolic factor 1 (hsCRP+TG+BMI) T1 Metabolic factor 2 (Chol+LDL) Age	-24.3(8.7) -14.3(6.8) 1.5(0.9)	-0.432 -0.255 0.264	0.007 0.037 0.072

1 High sensitivity C reactive protein

2 Triglycerides

3 Total cholesterol

4 Low Density Lipoprotein cholesterol